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Sex-based differences in brain alterations across chronic pain conditions

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Abstract

Common brain mechanisms are thought to play a significant role across a multitude of chronic pain syndromes. In addition, there is strong evidence for the existence of sex differences in the prevalence of chronic pain and in the neurobiology of pain. Thus, it is important to consider sex when developing general principals of pain neurobiology. The goal of the current review is to evaluate what is known about sex-specific brain alterations across multiple chronic pain populations. A total of 15 sex difference and 143 single-sex manuscripts were identified out of 412 chronic pain neuroimaging manuscripts. Results from sex difference studies indicate more prominent primary sensorimotor structural and functional alterations in female chronic pain patients compared to male chronic pain patients; differences in the nature and degree of insula alterations, with greater insula reactivity in male patients; differences in the degree of anterior cingulate structural alterations; and differences in emotional-arousal reactivity. Qualitative comparisons of male-specific and female-specific studies appear to be consistent with the results from sex difference studies. Given these differences, mixed-sex studies of chronic pain risk creating biased data or missing important information and single-sex studies have limited

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generalizability. The advent of large scale neuroimaging databases will likely aid in building a more comprehensive understanding of sex differences and commonalities in brain mechanisms underlying chronic pain.

Keywords

Neuroimaging; pain; sex differences

INTRODUCTION

Chronic pain describes pain that persists beyond a specific amount of time, usually at least 3 months beyond the normal healing period (Tsay et al. 2015), and includes a group of disorders such as irritable bowel disease (IBS), migraine, chronic headache, chronic lower back pain, fibromyalgia, vulvodynia, dysmenorrhea, and chronic prostatitis/chronic pain syndrome (Smith et al. 2014). The prevalence of chronic pain is growing in the population with current estimates that up to 64% report a chronic pain condition over their lifetime in the United States (Johannes et al. 2010). According to the Institute of Medicine, the health burden and health care costs to the individual and to society are increasing dramatically with estimates as high as $600 million each year in the United States (https://nccih.nih.gov/). Often chronic pain conditions are associated with increased disability, increased depression and anxiety, loss of income, and social isolation (Smith et al. 2014).

Chronic pain is complex, the investigation of pathophysiological mechanisms are still in progress, and existing treatments are suboptimal (Kawi 2015). The majority of studies investigating the pathophysiology of chronic pain have emphasized the origination of nociceptive signals in peripheral nerve terminal followed by encoding and modulation of these signals in the central nervous system (Aronoff 2016). More recently, multimodal neuroimaging studies have revealed abnormalities in evoked brain responses, morphology, and functional and anatomical connectivity in regions associated with salience, emotional arousal, and sensorimotor networks in patients with chronic pain (Mayer et al. 2015). It remains to be determined if these changes are primary nervous system alterations contributing to chronic pain, or if they are secondary brain changes resulting from ongoing nociceptive input to the central nervous system from the periphery.

Many chronic pain conditions are associated with a lowered pressure pain threshold in body locations far from the affected area, a sign of central sensitization. In addition, patients with chronic pain frequently have comorbidity with other chronic pain and psychiatric conditions, the precise location of the pain and predominant symptoms frequently change over time, and patients with different conditions show similar responses to centrally targeted therapies. Thus, common brain mechanisms, such as central sensitization, are thought to exist across a multitude of chronic pain syndromes (Mayer et al. 2009; Phillips and Clauw 2011). Consequently, there is increasing interest in identifying general principles of dysfunctional neurocircuitry associated with chronic pain states regardless of the particular body location affected. Furthermore, chronic pain syndromes demonstrate well-known sex differences in prevalence, severity, and response to treatment, with women typically showing greater

prevalence for many syndromes (Andersson et al. 1993; Barsky et al. 2001; Berkley 1997; Berkley et al. 2006). Sex is increasingly being understood as an important basic variable, influencing the quality and generalizability of biomedical research (Clayton 2016). Although men and women may be highly similar in the experience of pain, important sex differences exist at all levels in the signaling systems involved in pain processing and stress, suggesting major differences in the operation of pain mechanisms (Bale and Epperson 2015; Berkley 1997; Cahill 2006), as well as sex (biological) and gender (social) differences in behavioral responses to pain (Bartley and Fillingim 2013). Given these considerations, it is critical to incorporate potential sex differences in any development of general principles for understanding chronic pain. The goal of the current review is to lay the groundwork for this process by examining the current status of the empirical literature on sex-specific brain alterations across chronic pain populations.

METHODS

Manuscript identification

Literature searches were carried out in the Web of Science Core Collection (Thomson Reuters, New York) for neuroimaging studies of chronic pain populations published by December, 2015. The following chronic pain conditions impacting men and women were considered for this review: irritable bowel syndrome (IBS), functional dyspepsia, gastroesophageal reflux disease (GERD), migraine, cluster headache, tension type headache, temporomandibular disorder, burning mouth syndrome (BMS), atypical facial pain (AFP), chronic back/neck/shoulder/limb pain, osteoarthritis, whiplash, fibromyalgia, chronic widespread pain (CWP), chronic fatigue syndrome (CFS), urological chronic pelvic pain syndrome (UCPPS), and interstitial cystitis/painful bladder syndrome IC/PBS. In order to discern consistency in alterations across chronic pain disorders within sex, additional sex-specific chronic pain disorders (chronic prostatitis [CP], vulvodynia, vestibulitis, primary dysmenorrhea [PDM], premenstrual dysphoric disorder [PMDD], and endometriosis) were included in the review. These chronic pain conditions are all thought to have a strong central component (e.g., show pressure pain hypersensitivity) and are frequently co-morbid with other chronic pain conditions (Fernández-de-Las-Peñas et al. 2011; Herregods et al. 2015; Hsu et al. 2015; Li et al. 2013; Mayer et al. 2009; Phillips and Clauw 2011). Brain imaging techniques that were considered for the review included: structural magnetic resonance imaging (MRI), functional MRI (fMRI), positron emission tomography (PET), arterial spin labeling, diffusion tensor imaging (DTI), proton magnetic resonance spectroscopy (PMRS), and single-photon emission computed tomography (SPECT). Case reports, diagnostic neuroimaging, reviews, animal studies and treatment studies were excluded from consideration. Figure 1 depicts the manuscript selection process. A total of 412 potential manuscripts of interest were identified and further examined for their treatment of sex. Manuscripts with a focus on sex differences or sex hormones were identified by examination of the abstract and title. Single-sex studies were identified by examination of the title, abstract and methods section of the manuscript. Selected manuscripts were further classified in terms of evoked or non-evoked (or both) neuroimaging paradigms. Evoked paradigms use transient, experimental stimuli to identify changes in brain response (e.g. fMRI). Non-evoked paradigms focus on structural alterations in the brain (e.g. MRI, DTI), alterations in

metabolism or neurotransmitter activity (e.g. PET), or intrinsic activity/connectivity alterations (e.g. resting-state fMRI). Resting-state fMRI may be used to identify state-based changes (e.g. interictal vs. ictal in migraine research) in activity/connectivity, which may differ from transient, evoked changes. Each type of neuroimaging modality produces different information about the role of the brain in chronic pain.

RESULTS

The treatment of sex in the field of chronic pain neuroimaging

Out of 412 chronic pain neuroimaging manuscripts, a total of 15 sex difference (i.e., those comparing results for men and women), 143 single-sex, and 254 mixed-sex manuscripts were identified. Although some neuroimaging studies of menstrual-related pain disorders imaged across the menstrual cycle in order to compare a pain vs non-pain state, no manuscripts with a clear focus on sex hormones were identified. The proportion of sex-based studies for each of the pain conditions included in the literature search is shown in Figure 2. Sex difference manuscripts accounted for a small portion of the total literature (3.6%) and were concentrated in IBS and migraine research. A more substantial portion consisted of single-sex manuscripts (34.7%). These manuscripts tended to be segregated by pain diagnosis with studies in fibromyalgia, IBS, migraine, AFP, BMS, and IC/PBS mainly consisting of female-specific studies, while neuroimaging studies of cluster headache were exclusively male-specific. Furthermore, female-specific studies (n=129) vastly outnumbered male-specific studies (n=14).

Co-citation network analysis—To gain a better understanding of the popularity and extent of influence of sex-based studies in the field of chronic pain neuroimaging, a co-citation network analysis was performed using Pajek visualization software. Co-citation network analyses assume that bibliographic elements act as concept surrogates, thus references included in a paper are considered to reflect some influence on its findings (Casillas and Acedo 2007). Co-citation network analyses identify groups of closely related documents that can be considered as belonging to the same ‘research front’ as well as provide information about how different fronts interrelate. All 412 identified chronic pain neuroimaging manuscripts were entered into the analysis visualized in Figure 3, which also incorporates information regarding the total number of citations for each manuscript. Visual examination of the overall structure in Figure 3 reveals that greater affinity exists among IBS, fibromyalgia, and urological/pelvic pain neuroimaging researchers, than between these groups and migraine/headache researchers. In addition, the popularity of sex-based studies (both sex difference and single-sex studies) varied with sex-based studies fairly well-cited and well-connected within the IBS subfield, while many sex-based studies were poorly cited and not well-connected within the migraine and headache subfield.

DISCUSSION

Sex difference neuroimaging studies of patients with chronic pain suggest that across pain conditions sex differences exist in the altered reactivity, morphology, and connectivity of major brain regions and networks involved in pain modulation (Table 1). Although additional regions/networks demonstrate sex differences, below we summarize the findings

for three networks that, as of yet, comprise the majority of sex differences in chronic pain: salience, sensorimotor, and emotional-arousal networks. In addition to reviewing the findings from sex differences studies, the results from sex-specific studies (Supplementary Table 1) are also qualitatively evaluated for consistency with the sex difference studies.

Salience Network

The anterior cingulate (ACC; involved in emotion-cognitive interactions) and anterior insula (involved in the integration of interoceptive, affective, and cognitive influences) form the salience network, which functions to identify the most salient, homeostatically-relevant events among all internal and external stimuli (Menon and Uddin 2010). The salience network, through the anterior insula, also mediates the 'switching' between activation of the default mode network (DMN) and other major networks in order to guide appropriate responses to the salient event (Menon and Uddin 2010). The insula and the ACC have long been recognized as important to pain and to be involved in pain-related perceptual, affective, and cognitive responses (Derbyshire et al. 1997).

Sex-difference studies—Insula pain-related responses appear to be enhanced to a greater extent in male patients compared to female patients, at least in IBS and migraine pain populations, where direct comparisons have been made (Berman et al. 2000; Labus et al. 2013; Maleki et al. 2012a). Sex difference studies also indicate that sex influences the nature of insula alterations, at least in terms of intrinsic activity and connectivity (Gupta et al. 2014; Hong et al. 2013a; Hong et al. 2014; Jiang et al. 2013; Maleki et al. 2012b). In particular, altered connectivity between the insula and DMN may be more relevant to female pain patients than male patients, suggesting sex differences in internally-directed resources in response to stressful and salient events (Hong et al. 2014; Maleki et al. 2012b).

In contrast to the insula, ACC pain-related responses may be enhanced to a greater extent in female patients compared to male patients, at least in IBS (Naliboff et al. 2003). In addition, anatomical ACC alterations have been reported to be more prominent in female patients with IBS, with female patients demonstrating reduced subgenual ACC cortical thickness and increased mean diffusivity in cingulate white bundles compared to male patients (Ellingson et al. 2013; Jiang et al. 2013). However, male patients with IBS have demonstrated greater ACC reactivity to emotional stimuli previously shown to elicit greater behavioral and brain responses in healthy male subjects compared to healthy female subjects (Labus et al. 2013). Moreover, sex differences in altered ACC functional connectivity have been reported in both migraine and IBS studies, with enhanced ACC connectivity with emotional-arousal regions such as the amygdala and hippocampus in female patients with IBS compared with male patients (Gupta et al. 2014; Labus et al. 2013; Labus et al. 2008; Liu et al. 2011).

Single sex studies—Although pain-related insula reactivity may be enhanced to a greater degree in male patients than in female patients, single-sex studies demonstrate that both male and female patients in many chronic pain conditions show increased anterior/posterior insula responses to pain compared to same-sex healthy controls (Bannbers et al. 2012; Berman et al. 2008; Cook et al. 2004; Diers et al. 2011; Ellingson et al. 2012; Elsenbruch et al. 2010a; Elsenbruch et al. 2010b; Farmer et al. 2011; Hall et al. 2010; Hampson et al.

2013; Howard et al. 2012; Hubbard et al. 2015; Kim et al. 2011; Labus et al. 2013; Larsson et al. 2012; Lopez-Sola et al. 2014; Lowen et al. 2015; May et al. 1998b; McLoughlin et al. 2011; Pujol et al. 2009; Pukall et al. 2005; Rahm et al. 2015; Sprenger et al. 2007; Tu et al. 2010). Furthermore, female patients with FM show increased connectivity between insula and DMN regions, similar to female patients with IBS and migraine (Hong et al. 2014; Ichesco et al. 2014; Maleki et al. 2012b; Napadow et al. 2010), while altered insula connectivity of male patients with chronic prostatisis did not include DMN regions (Kutch et al. 2015). Additional male-specfic studies reporting altered insula connectivity were seed/region-specific and did not examine whether altered insula-DMN connectivity existed (Qiu et al. 2013; Qiu et al. 2012). Similar to the insula, both male and female patients have demonstrated increased ACC reactivity to pain relative to same-sex healthy controls (Hall et al. 2010; Howard et al. 2012; Larsson et al. 2012; Lowen et al. 2015; May et al. 1998a)Pujol 2009}(Albuquerque et al. 2006; Berman et al. 2008; Mayer et al. 2005). In addition, both male and female patients have demonstrated decreased ACC volume/density relative to same-sex healthy controls (As-Sanie et al. 2012; Burgmer et al. 2009; Jensen et al. 2013; Kuchinad et al. 2007; Mordasini et al. 2012; Robinson et al. 2011; Tu et al. 2013; Wood et al. 2009).

Interim summary—While single-sex studies demonstrate that insula and ACC pain reactivity is enhanced in both male and female patients with chronic pain relative to same-sex controls, sex difference studies show that important sex differences exist in the degree of of ACC structural alterations and the reactivity and functional organization of the insula and ACC in patients with chronic pain. Given the role of the insula and ACC in guiding the response to salient events, sex differences in altered reactivity and connectivity are likely to may impact vigilance, allocation of attentional resources and the mobilization of maladaptive processes in response to pain and stress in chronic pain patients.

Sensorimotor Network

The sensorimotor network includes the primary and secondary somatosensory and motor cortices as well as the basal ganglia. A recent neuroimaging study found a relationship between the cortical thickness of primary somatosensory cortex and pain thresholds in healthy controls, demonstrating an importance of primary somatosensory morphology in individual differences in pain sensitivity that may affect vulnerability to chronic pain (Erpelding et al. 2012).

Sex-difference studies—Sex difference studies suggest more prominent alterations exist in the primary sensorimotor cortex of female patients compared to male patients. In IBS, female but not male patients demonstrate increased cortical thickness of the sensorimotor cortex compared to same-sex controls (Jiang et al. 2013). Although a recent study did not find sex differences in the mean fractional anisotropy of all tracts innervating somatosensory cortex (Irimia et al. 2015), previous studies have shown reduced integrity of sensorimotor-related tracts in female IBS patients compared to male IBS patients (Ellingson et al. 2013; Woodworth et al. 2015). A potential reason for this discrepancy may be that sex differences occur within specific white matter tracts and this information is lost when averaging the fractional anisotropy across all tracts. In migraine patients, more dysfunctional connections

and decreased centrality in networks including sensorimotor have been found in female patients compared to male patients (Liu et al. 2011). Furthermore, female children with migraines demonstrate greater cortical thickness increases in primary somatosensory cortex with age compared to male children with migraines (Faria et al. 2015).

Sex differences in sensorimotor alterations also extend beyond the cortex. Specifically, female patients with migraines demonstrate more dysfunctional connections involving the caudate and putamen (Liu et al. 2015b) and greater pain-related reactivity in the caudate, while male patients with migraines demonstrate greater pain-related reactivity in the putamen (Maleki et al. 2012b). Furthermore, female children with migraines demonstrate increased gray matter volume in the caudate and pallidum, suggesting an organizational/chromosomal rather than a sex hormone driven mechanism (Faria et al. 2015). Finally, female IBS patients demonstrate lower fractional anisotropy and mean diffusivity in the globus pallidus compared with male IBS patients (Ellingson et al. 2013).

Single sex studies—Compared to female healthy controls, increased primary somatosensory cortical thickness/gray matter density/volume has been observed in female patients with migraine (Kim et al. 2014), IBS (Labus et al. 2014; Labus et al. 2015), IC/PBS (Kairys et al. 2015), FM (Fallon et al. 2013; Lutz et al. 2008), and UCPPS (Bagarinao et al. 2014). In addition, patients with dysmenorrhea demonstrate greater menstrual-related increases in primary somatosensory cortex gray matter volume compared to female healthy controls (Tu et al. 2013). Furthermore, additional primary sensorimotor cortical alterations including connectivity, intrinsic activity, reactivity, and perfusion have been noted in female-specific chronic pain studies (Arkink et al. 2012; Burgmer et al. 2012; Ellingson et al. 2012; Guedj et al. 2008; Guedj et al. 2007; Gupta et al. 2015; Kamping et al. 2013; Kilpatrick et al. 2014; Kim et al. 2013; Lee et al. 2013; Liu et al. 2015a; Liu et al. 2015b; Pujol et al. 2014; Rahm et al. 2015; Tu et al. 2009).

Although male-specific studies are severely limited, none have reported gray matter changes within the primary sensorimotor (Farmer et al. 2011; Mordasini et al. 2012). However, increased functional connectivity between motor cortices and the posterior insular has been reported in male patients with CP relative to same-sex healthy controls (Kutch et al. 2015). In addition, alterations of the internal capsule have been reported in male patients with cluster headaches relative to same-sex healthy controls (Teepker et al. 2012). Thus, some important sensorimotor alterations may exist in male patients.

Interim summary—While single-sex studies suggest that some sensorimotor alterations may exist in male patients with chronic pain, sex difference studies show more prominent structural changes in primary sensorimotor cortices and a greater number of altered sensorimotor/basal ganglia functional connections in female chronic pain patients compared to male patients. Sex differences in primary sensorimotor cortical alterations may impact the development of effective transcranial magnetic stimulation-based therapies for chronic pain. In addition, sex differences in chronic pain-related basal ganglia alterations could impact vulnerability to drug abuse and obesity (Geha et al. 2014).

Emotional-Arousal Network

The emotional-arousal network includes the amygdala, hippocampus/parahippocampal gyrus, and ACC (Pezawas et al. 2005; Stein et al. 2007). The amygdala has long been considered to play a role in the affective modulation of pain (Carrasquillo and Gereau 2007; Neugebauer et al. 2004). In addition, similarities between pain and memory mechanisms in the hippocampus have been reported (Price and Inyang 2015). The ACC has already been discussed above as a region of the salience network involved in emotion-cognitive interactions and findings relating to the ACC have been presented; therefore, the following sections mainly focus on findings related to the amygdala and hippocampus.

Sex-difference studies—Early sex difference studies in IBS suggested that emotional-arousal responses (amygdala and ACC) and altered connectivity were greater in female patients compared to male patients (Labus et al. 2008; Naliboff et al. 2003). However, subsequent studies have demonstrated that male IBS patients may have greater reactivity (amygdala, hippocampus, and ACC) under specific experimental conditions, such as when viewing faces depicting emotions previously shown to elicit greater behavioral and brain responses in male subjects (fear and anger) (Labus et al. 2013). Thus, male and female IBS patients may have similar or analogous changes in emotional-arousal reactivity, with sex-specific triggers. Sex difference studies in migraine research also call into question the notion that emotional-arousal reactivity is greater in female patients as women with migraines have demonstrated greater deactivation of emotional-arousal regions (amygdala and hippocampus) compared to male patients, at least to thermal pain stimuli (Maleki et al. 2012b).

Single sex studies—Both female- and male-specific studies have demonstrated increased emotional-arousal reactivity (amygdala and hippocampus) and altered connectivity during pain in patients compared to same-sex controls (Gingnell et al. 2012; Howard et al. 2012; Jensen et al. 2012; Kamping et al. 2013; Khan et al. 2014; Kim et al. 2013; Liu et al. 2015b; Liu et al. 2012; Martucci et al. 2015; May et al. 1998a; Mayer et al. 2005; Qiu et al. 2013; Sprenger et al. 2006; Wilder-Smith et al. 2004).

Interim summary—Both sex-specific and sex difference studies suggest that male and female patients demonstrate increased emotional-arousal reactivity to pain with altered functional organization of the amygdala and hippocampus relative to same-sex healthy controls. However, the conditions eliciting the enhanced response may differ between male and female patients.

Barriers to progress

Sex differences clearly exist in brain responses to experimental evoked pain but most of these studies have been performed in healthy controls and not in patients with chronic pain (reviewed in (Fillingim et al. 2009)). However, the study of sex differences in the response to evoked pain within chronic pain populations is critical. As of yet, it is not clear how sex differences in the brain's functional response to acute, experimental pain in healthy controls relates to the noted sex differences in chronic pain prevalence, symptoms, and response to treatment.

Furthermore, while the reported sex-specific structural brain changes are likely to contribute to the observed clinical and epidemiological sex differences in chronic pain, for the majority of chronic pain conditions, sex difference neuroimaging research is lacking. Rather, researchers either report mixed-sex studies or attempt to control for sex-based biology by focusing on a single sex (usually female). One result of this strategy is that male subjects are severely underrepresented. Although chronic pain is more prevalent in women, there are still substantial numbers of men suffering from chronic pain. The sex difference studies that have been conducted show that important sex differences exist in chronic pain. Thus, mixed- and single-sex studies of chronic pain have limited generalizability, risk creating biased data, and may miss important findings. For example, in Hong et al (Hong et al. 2013b), when sex was ignored, no differences in insula activity were found between IBS patients and healthy controls. When sex difference analyses were performed, it was found that insula low frequency power was increased in male patients with IBS and decreased in female patients compared to same-sex healthy controls. Controlling for sex would not have allowed this discovery. Another consequence of focusing on one sex within a particular pain condition is that only half the picture is being generated for that condition, which limits the generation of potentially fruitful scientific questions. The direct comparison of men and women offers a unique perspective, which can provide the critical spark that ignites fundamental breakthroughs (McCarthy et al. 2012).

Another potential barrier concerns bias in the diagnostic criteria for some chronic pain conditions. For example, the symptom criteria for fibromyalgia as defined by the American College of Rheumatology emphasizes the number of trigger points which may contribute to a female bias as women appear to innately have more tender points than men (Berkley 1997; Vincent et al. 2013a), thus subject recruitment for an adequately powered sex difference study is difficult. A more general view that focuses on the presence of chronic widespread pain (CWP) shows much less sex-bias (LeResche 1999). Given the demonstrated differences in men and women with other types of chronic pain, it appears likely that females with fibromyalgia should not represent all CWP patients. In another example, new thinking in pelvic pain has created a more inclusive diagnosis of urologic chronic pelvic pain syndrome (UCPPS), which incorporates what have previously been considered separate male and female syndromes. Previously, the female version was called interstitial cystitis/painful bladder syndrome (IC/PBS), and the male version was called chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). Thus sex difference studies in UCPPS would greatly add to the understanding of commonalities and differences in pelvic pain. Finally, chronic back pain is one of the most common pain conditions and affects both men and women, yet sex difference neuroimaging studies are lacking. Thus, neuroimaging studies of sex differences are feasible in a wide range of chronic pain conditions, but have not yet been realized. An important clinical consequence of identifying neurobiological sex differences in chronic pain patients is the concept that different brain mechanisms may play a role in the construction of the chronic pain experience, which in turn may require sex-specific treatment approaches to male and female patients.

An additional area in which a lack of research may be creating a barrier to progress concerns sex hormones. Sex hormones are well known to influence pain perception with estradiol having both pro-nociceptive and anti-nociceptive actions while testosterone appears to be

mainly anti-nociceptive in both males and females (Aloisi and Bonifazi 2006; Craft 2007; Vincent and Tracey 2010). While the importance of studying sex hormone-related effects is most obvious in menstrual pain-related syndromes, many other chronic pain patients demonstrate cycle-related or menopausal-related changes in symptom severity (Heitkemper and Chang 2009; Martin 2009). Although a few neuroimaging studies have imaged across the menstrual cycle in menstrual-related pain populations, the focus was on high and low pain states, not the role of sex hormones in chronic pain (Tu et al. 2009; Tu et al. 2013; Vincent et al. 2011). Results from a recent neuroimaging study using healthy women suggest that in a low endogenous estradiol state, testosterone may be a key factor in modulating pain sensitivity via descending pathways of the brain with higher levels of endogenous testosterone associated with decreased thermal pain sensitivity (Vincent et al. 2013b). Thus, sex hormones affect pathways potentially important to chronic pain.

Conclusions and Future Directions

This review demonstrated that, when examined, significant sex differences exist in the altered morphology, connectivity, and response to pain in the brain of chronic pain patients. Sex difference studies indicate more prominent primary sensorimotor structural and functional alterations in female chronic pain patients compared to male chronic pain patients; differences in the nature and degree of insula alterations, with greater insula reactivity in male patients; differences in the degree of anterior cingulate structural alterations; and differences in emotional-arousal reactivity that be driven mainly by sex differences in the effectiveness of emotional-arousal triggers. Qualitative comparisons of male-specific and female-specific studies appear to be consistent with the results from sex difference studies.

Sex difference research has been concentrated in few pain disorders, and the large number of single-sex studies are severely imbalanced, favoring female chronic pain patients. In addition, the co-citation analysis revealed areas in which sex-based research and collaboration is needed. Much work is still needed to advance a neurobiological understanding of the differences between male and female chronic pain patients with the goal of improving chronic pain for both men and women. Big data efforts, such as the recently developed PAIN neuroimaging database (PainRepository.org), which contains neuroimaging scans from a wide variety of pain patients and healthy controls, can provide the sample sizes needed to facilitate analyses leading to a more comprehensive understanding of the commonalities and differences in brain alterations of male and female patients across chronic pain conditions, particularly with the use of standardized imaging protocols (Labus et al. 2016).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Significance

Chronic pain disorders are associated with a great burden to the individual and to society. Brain alterations are involved in chronic pain and recent developments suggest that common mechanisms may exist across a multitude of chronic pain conditions. In addition, sex differences exist at all levels in the signaling systems involved in pain processing and stress. This review summarizes what is known about sex-specific brain alterations found across chronic pain populations and where additional research is needed. These findings have implications for the development of effective treatments for both male and female patients with chronic pain.

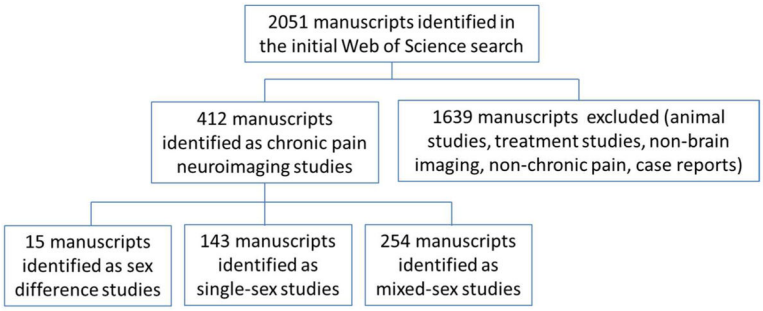

Figure 1.
The manuscript selection process is depicted.

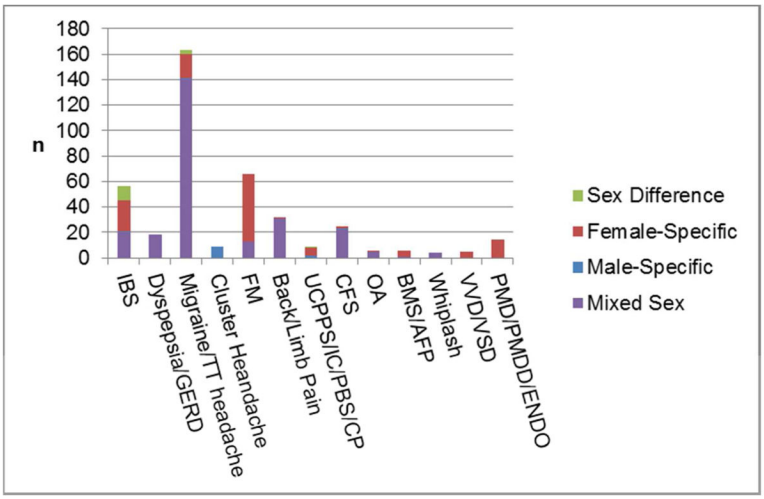

Figure 2.

The number of manuscripts as classified in terms of the treatment of sex is shown for the chronic pain conditions included in the review. IBS, irritable bowel syndrome; GERD, gastroesophageal reflux disease; TT: tension-type; FM, fibromyalgia; UCPPS, urological chronic pelvic pain syndrome; IC/PBS, interstitial cystitis/painful bladder syndrome; CP, chronic prostatitis; CFS, chronic fatigue syndrome; OA, osteoarthritis; BMS, burning mouth syndrome; AFP, atypical facial pain; VVD, vulvodynia; VVS, vulvar vestibulitis syndrome; PDM, primary dysmenorrhea; PMDD, premenstrual dysphoric disorder; ENDO, endometriosis. No temporomandibular disorder manuscripts were identified.

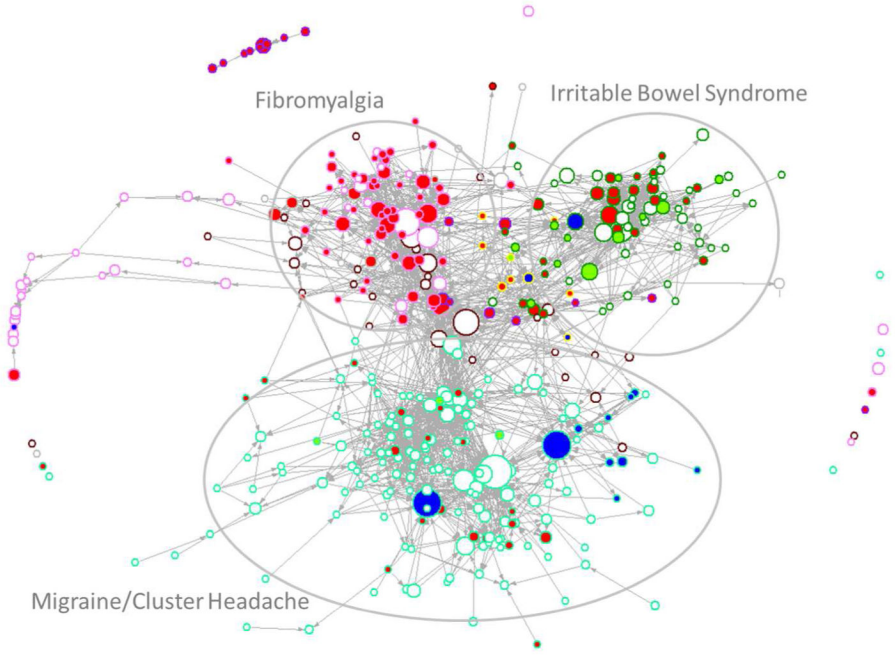

Figure 3.

A co-citation network analysis of chronic pain neuroimaging studies with a focus on the treatment of sex is depicted. Each manuscript of interest was coded according to its treatment of sex (represented by the color of the inside of the associated vertex: green, sex differences; red, female-specific; blue, male-specific; white, mixed-sex) and pain population (represented by the color of the vertex border: gastrointestinal, dark green; fibromyalgia and chronic fatigue syndrome, lavender; chronic back/limb pain, brown; urological pain, yellow; headache pain, teal; menstrual and vulvar pain, purple; other, gray). The size of each vertex was determined by the total number of citations the manuscript received by December 2015. Examination of Figure 3 indicates a fair degree of cross-citation among chronic pain neuroimaging researchers of different pain conditions, but less so for headache pain studies. The largest cluster in the figure (lower center) represents mainly migraine and cluster headache studies where despite the existence of sex difference manuscripts, sex appears to be generally not well-considered.

Table 1

Sex difference publications listed by year of publication.

Sex Difference Publications				
Publication	**Populations**	**Modality/Task**	**Main Results**	**Evoked vs. Non-evoked Paradigm**
2015				
Faria et al 2015	All Children: Female Migr = 14 Male Migr = 14 Female HC = 14 Male HC = 14	MRI (CT, GMV)	Female Migr vs. Male Migr & HCs • Female patients had ↑ CT in SI, SMA, precuneus • Female patients had ↑ GMV in caudate, AMYG, pallidum	Non-evoked paradigm
Irimia et al 2015	Males IBS = 19 Females IBS = 14 Males HC = 23 Females HC= 33	DTI (FA)	Male & Female IBS vs Male & Female HC • mean FA of white matter bundles innervating S1 distinguished IBS from HC with no sex differences	Non-evoked paradigm
Woodworth et al 2015	Male UCPPS =26 Female UCPPS = 19 Male IBS =16 Female IBS = 23 Male HC= 30 Female HC = 26	DTI	Female UCPPS vs. Male UCPPS • Sex differences seen in HCs or IBS were not present in UCPPS Female IBS vs. Male IBS • Female patients had ↓ FA in the thalamus and BG • Female patients had ↑ MD in BG, coronal radiata, thalamic regions, brainstem, and corpus callosum • Female patients had ↓MD in SM	Non-evoked paradigm
2014				
Gupta et al 2014	Female IBS = 28 Male IBS = 30 Female HC = 72 Male HC = 38	Resting fMRI (ICA)	Male IBS vs. Male HC • Male patients had ↑ levels of early life adversities associated with ↑ connectivity of thalamus, INS, ACC, cerebellum, and MTG with the cerebellar network Female IBS vs. Female HC • No significant correlations were observed with ↑ levels of early life adversities in female subjects	Non-evoked paradigm
Hong et al 2014	Female IBS = 24 Male IBS = 24 Female HC = 24 Male HC = 24	Resting fMRI (functional connectivity of the dorsal aINS)	Female IBS vs. Female HC • Female patients had ↑ negative connectivity of dorsal aINS with mPFC Female IBS vs. Male IBS	Non-evoked paradigm

Sex Difference Publications				
Publication	**Populations**	**Modality/Task**	**Main Results**	**Evoked vs. Non-evoked Paradigm**
			• Male patients had ↑ positive connectivity of dorsal aINS with mPFC correlated with the Visceral Sensitivity Index • Female patients had ↑ negative connectivity of dorsal aINS with precuneus correlated with symptom intensity	
2013				
Ellingson et al 2013	Female IBS = 21 Male IBS = 12 Female HC = 72 Male HC = 21	DTI (FA, MD)	Female IBS vs. Male IBS • Female patients had ↓ FA in the thalamus and in primary sensory and motor regions • Female patients had ↑ MD in the coronal radiata, thalamic regions, and cingulate white matter bundles • Female patients had ↓MD in the globus pallidus	Non-evoked paradigm
Hong et al 2013	Female IBS = 31 Male IBS = 29 Female HC = 76 Male HC = 42	Resting fMRI (fALFF)	Female IBS vs. Female HC • Female patients showed ↑ frequency power distribution toward high frequency in the aINS and AMYG • Female patients had ↑ frequency power distribution toward low frequency in sensorimotor regions Male IBS vs. Male HC • Male patients showed ↓ frequency power distribution toward high frequency in the INS Female IBS vs. Male IBS • Female patients had ↑ frequency power distribution toward high frequency in INS, AMYG and HIPP • Female patients had ↑ frequency power distribution toward low frequency in PreCG, SI, SMA	Non-evoked paradigm
Jiang et al 2013	Female IBS = 70 Male IBS = 20 Female HC = 155 Male HC = 21	MRI (CT)	Female IBS vs. Female HC • Female patients had ↑ CT in SI, PreCG and ↓ CT in INS and sgACC Male IBS vs. Male HC • No significant differences observed Female IBS vs. Male IBS • Female patients had ↓ CT in sgACC	Non-evoked paradigm

Sex Difference Publications				
Publication	**Populations**	**Modality/Task**	**Main Results**	**Evoked vs. Non-evoked Paradigm**
Labus et al 2013	Female IBS = 27 Male IBS = 20 Female HC = 38 Male HC = 29	fMRI (non-painful emotional stimuli)	(Male IBS - Female IBS) vs. (Male HC – Female HC) • Patients had ↑ sex differences in activation of INS, pgACC, mPFC Male IBS vs. Female IBS • Male patients had ↑ activation in PFC, ACC, INS, PCC, HIPP, HYPO, NAcc • Male patients had ↑ connectivity among emotional-arousal regions including ACC and AMYG Male IBS vs. Male HC • Male patients showed ↑ activation in AMYG Female IBS vs. Female HC • No significant differences observed	Evoked non-pain paradigm
2012				
Maleki et al 2012	Female Migr = 11 Male Migr = 11 Female HC = 11 Male HC = 11	MRI (CT, GMV); fMRI (thermal pain + 1°C stimuli)	Female Migr vs. Female HC (Structural) • Female patients had ↑ CT in pINS and precuneus Male Migr vs. Male HC (Structural) • Male patients had↓ GMV in the PHG Female Migr vs. Male Migr (Pain response) • Female patients had ↑ activity in caudate, STG, SFG, precuneus and PCC and ↑ deactivation in AMYG and HIPP • Male patients had ↑ activity in INS, SI and putamen and ↑ deactivation in NAcc • Female patients had ↑ connectivity between INS and SI, PCC, precuneus, temporal pole • Female patients had ↑ connectivity between precuneus and SI, AMYG	Both evoked pain paradigm and non-evoked paradigm
2011				
Liu et al 2011	Female Migr = 20 Male Migr = 18 Female HC = 20 Male HC = 18	• Resting fMRI (topological properties)	Female Migr vs. Male Migr • Female patients had ↓ network resilience, ↓ nodal centrality (PreCG, dorsal SFG, inferior OFG, ACC, PHG) and ↑ dysfunctional connections (orbital PFC, PCC, PHG, cuneus,	Non-evoked paradigm

Sex Difference Publications				
Publication	**Populations**	**Modality/Task**	**Main Results**	**Evoked vs. Non-evoked Paradigm**
			putamen, caudate, parietal lobule, temporal lobes, occipital cortex)	
2008				
Labus et al 2008	Female IBS = 24 Male IBS = 22	PET (rectal balloon distension)	Female IBS vs. Male IBS: Emotional-arousal network: • During expectation of the balloon distention, the amygdala→iACC→sACC→ →pons/LCC circuits showed ↑ positive connectivity for female patients and negative or nonsignificant connectivity in male patients Homeostatic-afferent network: • During expectation of the balloon distention, INS connectivity to mOFC was consistently negative in male patients and more positive in female patients Cortical-modulatory network: • During baseline and expectation of the balloon distention, male patients showed ↑ positive connectivity between the pINS→AMYG, and female patients showed ↓ connectivity or lack of engagement of this circuit. • During inflation of the balloon and expectation of the balloon distention, female patients showed a strong positive connectivity between mOFC→ AMYG, whereas male patients demonstrated weak negative connectivity in this circuitry	Evoked pain paradigm
2003				
Nakai et al 2003	Female IBS = 6 Male IBS = 6 Female HC = 7 Male HC = 6	PET (5-HT synthesis)	Female IBS vs. Female HC • Female patients had ↑ 5-HT synthesis in MTG Male IBS vs. Male HC • No significant differences observed	Non-evoked paradigm
Naliboff et al 2003	Female IBS = 23 Male IBS = 19	PET (rectal balloon distension)	Female IBS vs. Male IBS • Female patients had ↑ activation in AMYG and ACC • Male patients had ↑ activation in dlPFC, dorsal pons/PAG and midposterior INS	Evoked pain paradigm
2000				

Sex Difference Publications				
Publication	**Populations**	**Modality/Task**	**Main Results**	**Evoked vs. Non-evoked Paradigm**
Berman et al 2000	Female IBS = 13 Male IBS = 17	PET (rectal distension)	Female IBS vs. Male IBS • Male patients had ↑ activation in INS	Evoked pain paradigm

Abbreviations - Groups: HC, healthy controls; IBS, irritable bowel syndrome; MIGR, migraine; UCPPS, urological chronic pelvic pain

Abbreviations – Methods: CT, cortical thickness; DTI, diffusion tensor imaging; FA, fractional anisotropy; fMRI, functional magnetic resonance imaging; GMD, grey matter density; GMV, grey matter volume; MD, mean diffusivity; MRI, magnetic resonance imaging; PET, positron emission tomography

Abbreviations – Brain Regions: ACC, anterior cingulate cortex; aINS, anterior insula; AMYG, amygdala; BG, basal ganglia; dlPFC, dorsal lateral prefrontal cortex; HIPP, hippocampus; HYPO, hypothalamus; INS, insula; mPFC, medial prefrontal cortex; MTG; middle temporal gyrus; NAcc, nucleau accumbens; OFC, orbital frontal cortex; OFG, orbital frontal gyrus; PAG, periaqueductal gray; PCC, posterior cingulate cortex; PFC, prefrontal cortex; pgACC, pregenual anterior cingulate cortex; PHG, parahippocampal gyrus; pINS, posterior insula; PreCG, precentral gyrus; SI, primary somatosensory cortex; SFG, superior frontal gyrus; sgACC, subgenual anterior cingulate cortex; SMA, supplementary motor area; STG, superior temporal gyrus; THAL, thalamus